PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

10/510383

Applicant's or agent's file reference Cal 86062	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/03784	International filing date *(day/month/year)* 11.04.2003	Priority date *(day/month/year)* 17.04.2002

International Patent Classification (IPC) or both national classification and IPC
C07C69/734

Applicant
ISAGRO RICERCA S.R.L.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 11 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11.11.2003	02.07.2004

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Seelmann, M

Telephone No. +49 89 2399-8335

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/03784

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-43 as originally filed

Claims, Numbers

1-23 received on 27.02.2004 with letter of 26.02.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-3,6-12,15-23
Inventive step (IS)	Yes:	Claims	
	No:	Claims	4,5,13,14
Industrial applicability (IA)	Yes:	Claims	1-23
	No:	Claims	

2. Citations and explanations

see separate sheet

Item V

Reasoned statement under Artikel 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1 US 5 145 980
D2 US 55 45 664
D3 EP 0 398 692 cited in the present application

V.3 Amendments

The definition provided in the amended claim 1 concerning the A parameter fullfills the requirements of article 6 PCT.

The present claim 1 was modified such that the scope has been reduced to compounds of formula (I) wherein:

X_1, X_5 = H; X_2, X_4 = Hal; X_3 = R;
or X_1, X_4 = H; X_3, X_5 = Hal; X_2 = R;
with Z = CH or N when Y = OCH_3 or Z = N when Y = $NHCH_3$.

These amendments correspond to the exclusion of the following originally disclosed possibilities:

1/ X_1 = Hal or R
2/ X_2 = H
3/ X_1, X_3 = H; X_2 = R
4/ X_1 = H; X_2, X_4, X_5 = Hal
5/ Z = CH when Y = $NHCH_3$.

The novelty-destroying compounds known from **D1** cover X_1, X_5 = Cl, F. Br; X_3 = Me or X_3, X_5 = Cl, F, Br; X_1 = R for the same activity as fungicides (*i.e.* disclaimer not allowable). The application as originally filed disclosed X_1, X_5 = H; X_2, X_4 = Hal; X_3 = R in the case n = 0 (claim 4 or page 4).

Accordingly there seems to be no support for the proposed amendments. These latter seem to be a generalization of the examples, contravening to the requirements of article 34(2)b) PCT.

Therefore the following issues of novelty and inventive step were dealt according to the original set of claims.

V.2 Novelty

As already outlined in the description, the teaching of **D3** (claim 2) can be seen as generic in regards to the present application. The phenoxymethylphenyl derivatives of general formula (I) presently claimed are already known from the prior art, for instance:

D1: compounds N°1.197 to 1.202 in table 1

Accordingly the subject-matters of claims 1-3, 6-12 and 15-23 are not novel in view of **D1**.

V.3 Inventive step

The closest state of the art for the present application is represented by **D1** disclosing structurally similar compounds which do not fall under the present application (claim 4) because of only the halogen positions on the phenyl ring: 2,6- or 2,4- (**D1**: compounds N°1.197 to 1.202) instead of 3,5-substitution in the present application (claim 4). Presently such a structural variation is alleged to lead to derivatives with the same qualitative activity/properties as those described in **D1**. In view of the experimental part and the other information as given in the description, it can be assumed that this problem has been solved for those compounds, wherein n = 0, $X_1 = X_5 = H$, $X_2 = X_4 = Cl$ and $X_3 = R$, *i.e.* an alkoxy, alkoxyalkyl, alkenyloxy, cycloalkylalkoxy and benzyloxy groups with possible halogen substitution or n = 0, $X_1 = X_4 = H$, $X_3 = X_5 = Cl$ and X_2 = alkylenoxy substituted by halogen (cf. letter of applicant of 26.02.2003, table on pages 3-4).

The problem underlying the present application can, however, not be seen in the provision of further novel derivatives, because in view of the extremely close structural relationship to **D1** compounds it is considered that the man skilled in the art would regard the new compounds of this application (claim 4) as being obvious alternatives to the known compounds.

Therefore, the problem underlying the present application should be seen in the provision of new derivatives having unexpected properties over those of the closest prior art compounds (**D1**). Comparative tests were performed between compounds 1.197 and 1.200 of **D1** with those claimed in the present application (cf. letter of applicant of 26.02.2003, table on pages 3-4).

It was convincingly shown, as previously stated, that the modified position of the halogen-substitution with simultaneous presence of an oxy-moiety on the phenyl ring improves dramatically the fungicidal activity. Therefore if one has to make use of the argument that

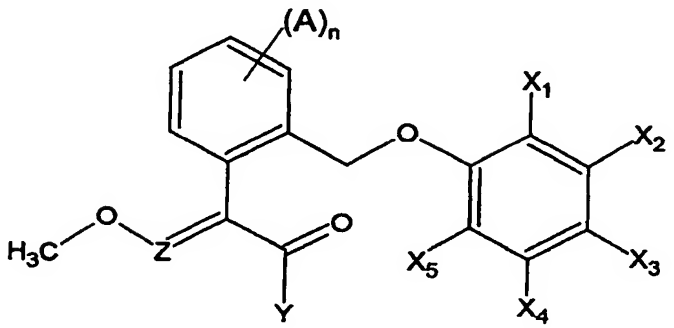
such a "minor" structural modifications could not be anticipated by the man skilled in the art to have such an influence on the sought activity, other more dramatic modifications as described in claim 1 cannot be considered as obvious or generalize without additional experimental evidence. Such a generalization could also lead to compounds having no effect at all. Accordingly only a reasonable generalization of the examples, not contravening to article 34(2)b) PCT, could be considered as inventive. Expressions such as heteroaryloxy or alkoxyiminoalkylidenoxy can be considered as a reasonable generalization, for instance !

The subject-matter of claim 4 and dependent claim 5 or related claims 13-14 do not therefore fulfill the requirements of Article 33(3) PCT.

Further comments:
The term "etc" is indefinite (cf. PCT Guidelines CIII-4.3a).

CLAIMS

1. Compounds having general formula (I)



(I)

wherein:

- X_1 represents a hydrogen atom;
- X_2 represents a halogen atom or an R group;
- X_3 represents an R group when X_2 = halogen, or represents a halogen atom when X_2 = R;
- X_4 represents a halogen atom when X_3 = R, or represents a hydrogen atom when X_2 = R;
- X_5 represents a hydrogen atom when X_3 = R, or represents a halogen atom when X_2 = R;
- R represents a C_1-C_{12} alkoxy or alkylthio group optionally substituted by halogen atoms, cyano groups, C_1-C_6 alkoxy groups optionally halogenated, C_2-C_{10} alkoxyalkoxy groups optionally halogenated, C_3-C_{12} trialkyl silyl groups; a C_2-C_{12} alkenyloxy or alkenylthio group optionally substituted by halogen atoms; a C_3-C_{12} alkynyloxy or alkynylthio group; a linear or branched C_3-C_{12} alkoxyimi-

noalkylidenoxy or alkoxyiminoalkylidenthio group; a C_3-C_8 cycloalkoxy group optionally substituted by halogen atoms, C_1-C_6 alkyl or haloalkyl groups; a C_4-C_{12} cycloalkylalkoxy or cycloalkylalkylthio group optionally substituted by halogen atoms, C_1-C_6 alkyl or haloalkyl groups; an aryloxy, arylthio, heteroaryloxy, heteroarylthio, aryl-(C_1-C_6)alkoxy, aryl-(C_1-C_6)alkylthio group optionally substituted by halogen atoms, C_1-C_6 alkyl groups optionally halogenated, C_1-C_6 alkoxy groups optionally halogenated, nitro groups, cyano groups;

- A represents a halogen atom or a C_1-C_4 alkyl, haloalkyl, alkoxy, haloalkoxy group, groups A being the same or different when n is greater than or equal to 2;
- Y represents an OCH_3 group or an $NHCH_3$ group;
- Z represents a CH group or a nitrogen atom N when Y = OCH_3, a nitrogen atom N when Y = $NHCH_3$;
- n is an integer ranging from 0 to 4.

2. The compounds according to claim 1, characterized in that they are an isomeric mixture in any proportion, or the isomer E or the isomer Z of the compounds having formula (I).

3. The compounds according to claim 1, characterized in that they are the isomer E of the compounds having formula (I).

4. The compounds according to claim 1, characterized in

that X_3 represents an R group according to the above mentioned meanings, X_2 and X_4 represent a halogen atom, X_1 and X_5 represent a hydrogen atom and n is equal to 0.

5. The compounds according to claim 1, characterized in that they are selected from:

- methyl (*E*)-2-[2-(4-cyclopropylmethoxy-3,5-dichlorophenoxymethyl)phenyl]-3-methoxyacrylate;
- methyl (*E*)-2-[2-(4-cyclopropylmethoxy-3,5-dichlorophenoxymethyl)phenyl]-2-methoxyiminoacetate;
- (*E*)-2-[2-(4-cyclopropylmethoxy-3,5-dichlorophenoxymethyl)phenyl]-N-methyl-2-methoxyiminoacetamide;
- methyl (*E*)-2-{2-[4-(2,2-dichlorocyclopropyl)methoxy-3,5-dichlorophenoxymethyl]phenyl}-3-methoxyacrylate;
- methyl (*E*)-2-{2-[4-(2,2-dichlorocyclopropyl)methoxy-3,5-dichlorophenoxymethyl]phenyl}-2-methoxyiminoacetate;
- (*E*)-2-{2-[4-(2,2-dichlorocyclopropyl)methoxy-3,5-dichlorophenoxymethyl]phenyl}-N-methyl-2-methoxyiminoacetamide;
- methyl (*E*)-2-{2-[3,5-dichloro-4-(3,3-dichloroprop-2-enyloxy)phenoxymethyl]phenyl}-3-methoxyacrylate;
- methyl (*E*)-2-{2-[3,5-dichloro-4-(3,3-dichloroprop-2-enyloxy)phenoxymethyl]phenyl}-2-methoxyiminoacetate;
- (*E*)-2-{2-[3,5-dichloro-4-(3,3-dichloroprop-2-enyloxy)-phenoxymethyl]phenyl}-N-methyl-2-methoxyiminoacetamide;
- methyl (*E*)-2-{2-[3,5-dichloro-4-(3-chloro-4,4,4-

trifluorobut-2-enyloxy)phenoxymethyl]phenyl}-3-methoxy-acrylate;

- methyl (*E*)-2-{2-[3,5-dichloro-4-(3-chloro-4,4,4-trifluorobut-2-enyloxy)phenoxymethyl]phenyl}-2-methoxyiminoacetate;

- (*E*)-2-{2-[3,5-dichloro-4-(3-chloro-4,4,4-trifluorobut-2-enyloxy)phenoxymethyl]phenyl}-N-methyl-2-methoxyiminoacetamide;

- methyl (*E*)-2-[2-(4-cyclobutylmethoxy-3,5-dichlorophenoxymethyl)phenyl]-3-methoxyacrylate;

- methyl (*E*)-2-{2-[3,5-dichloro-4-(3,3-dimethylbutoxy)phenoxymethyl]phenyl}-3-methoxyacrylate;

- methyl (*E*)-2-{2-[3,5-dichloro-4-(3-methylbutoxy) phenoxymethyl]phenyl}-3-methoxyacrylate;

- methyl (*E*)-2-[2-(4-cyclohexylmethoxy-3,5-dichlorophenoxymethyl]phenyl}-3-methoxyacrylate;

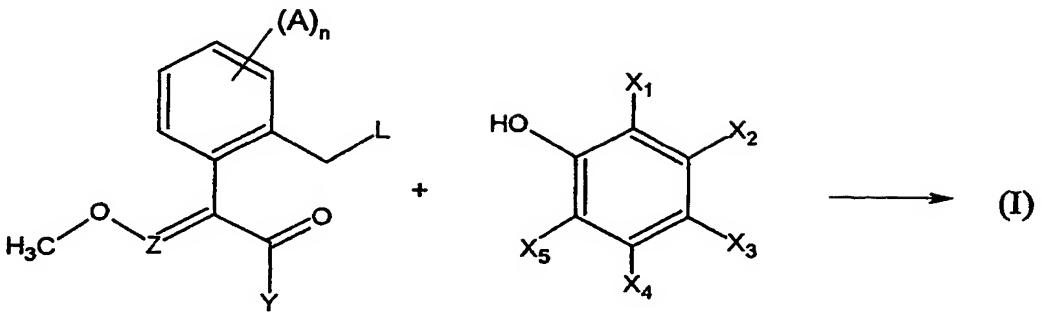
- methyl (*E*)-2-{2-[3,5-dichloro-4-(2,4-dichlorobenzyloxy)phenoxymethyl]phenyl}-3-methoxyacrylate;

- methyl (*E*)-2-{2-[3,5-dichloro-4-(4-chlorobenzyloxy)phenoxymethyl]phenyl}-3-methoxyacrylate.

6. The process for the preparation of the compounds having general formula (I), according to any of the claims 1-5, characterized in that it includes a condensation reaction of a compound having general formula (II) with a phenol having general formula (III), according to

the reaction scheme 1:

Scheme 1



(II) (III) (I)

wherein , X_1, X_2, X_3, X_4, X_5, A, Y, Z and n have the meanings defined above, L represents a leaving group such as a chlorine atom, a bromine atom or a $R_LSO_3^-$ group wherein R_L represents a C_1-C_6 alkyl or haloalkyl, or a phenyl optionally substituted.

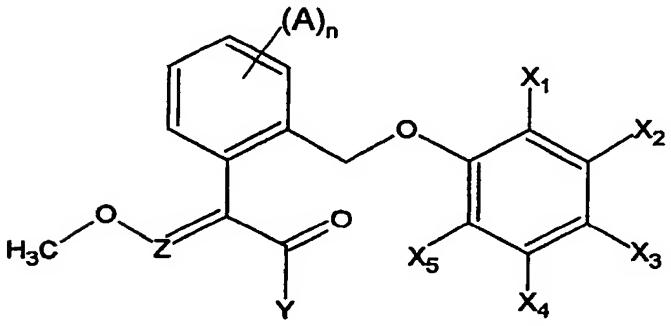
7. The process according to claim 6, characterized in that the reaction is carried out in an inert organic solvent, at a temperature ranging from 0°C and the boiling temperature of the reaction mixture, possibly in the presence of an inorganic or organic base.

8. The process according to claim 7, characterized in that the solvent is selected from alcohols, ethers, esters, ketones, chlorinated hydrocarbons, aromatic hydrocarbons, aliphatic hydrocarbons, aprotic dipolar solvents.

9. The process according to claim 7, characterized in that the inorganic base is selected from hydrides, hydroxides, carbonates of alkaline or alkaline-earth metals.

10. The process according to claim 7, characterized in that the organic base is selected from pyridine, dimethylaminopyridine, aliphatic amines, cyclic amines, alcoholates of alkaline metals.

11. Use of the compounds having general formula (I)



(I)

wherein:

- X_1 represents a hydrogen atom;
- X_2 represents a halogen atom or an R group;
- X_3 represents an R group when X_2 = halogen, or represents a halogen atom when X_2 = R;
- X_4 represents a halogen atom when X_3 = R, or represents a hydrogen atom when X_2 = R;
- X_5 represents a hydrogen atom when X_3 = R, or represents a halogen atom when X_2 = R;

- R represents a C_1-C_{12} alkoxy or alkylthio group optionally substituted by halogen atoms, cyano groups, C_1-C_6 alkoxy groups optionally halogenated, C_2-C_{10} alkoxyalkoxy groups optionally halogenated, C_3-C_{12} trialkyl silyl groups; a C_2-C_{12} alkenyloxy or alkenylthio group optionally substituted by halogen atoms; a C_3-C_{12} alkynyloxy or alkynylthio group; a linear or branched C_3-C_{12} alkoxyiminoalkylidenoxy or alkoxyiminoalkylidenthio group; a C_3-C_8 cycloalkoxy group optionally substituted by halogen atoms, C_1-C_6 alkyl or haloalkyl groups; a C_4-C_{12} cycloalkylalkoxy or cycloalkylalkylthio group optionally substituted by halogen atoms, C_1-C_6 alkyl or haloalkyl groups; an aryloxy, arylthio, heteroaryloxy, heteroarylthio, aryl-(C_1- C_6)alkoxy, aryl-(C_1-C_6)alkylthio group optionally substituted by halogen atoms, C_1-C_6 alkyl groups optionally halogenated, C_1-C_6 alkoxy groups optionally halogenated, nitro groups, cyano groups;

- A represents a halogen atom or a C_1-C_4 alkyl, haloalkyl, alkoxy, haloalkoxy group, groups A being the same or different when n is greater than or equal to 2;

- Y represents an OCH_3 group or an $NHCH_3$ group;

- Z represents a CH group or a nitrogen atom N when Y = OCH_3, a nitrogen atom N when Y = $NHCH_3$;

- n is an integer ranging from 0 to 4;

as acaricides and/or insecticides and/or fungicides.

12. The use according to claim 11 of the isomers E of the compounds having formula (I).

13. The use according to claim 11, wherein X_3 represents an R group according to the above meanings, X_2 and X_4 represent a halogen atom, X_1 and X_5 represent a hydrogen atom and n is equal to 0.

14. The use according to claim 11, wherein the compounds of formula (I) are selected from:

- methyl (*E*)-2-[2-(4-cyclopropylmethoxy-3,5-dichlorophenoxymethyl)phenyl]-3-methoxyacrylate;
- methyl (*E*)-2-[2-(4-cyclopropylmethoxy-3,5-dichlorophenoxymethyl)phenyl]-2-methoxyiminoacetate;
- (*E*)-2-[2-(4-cyclopropylmethoxy-3,5-dichlorophenoxymethyl)phenyl]-N-methyl-2-methoxyiminoacetamide;
- methyl (*E*)-2-{2-[4-(2,2-dichlorocyclopropyl)methoxy-3,5-dichlorophenoxymethyl]phenyl}-3-methoxyacrylate;
- methyl (*E*)-2-{2-[4-(2,2-dichlorocyclopropyl)methoxy-3,5-dichlorophenoxymethyl]phenyl}-2-methoxyiminoacetate;
- (*E*)-2-{2-[4-(2,2-dichlorocyclopropyl)methoxy-3,5-dichlorphenoxymethyl]phenyl}-N-methyl-2-methoxyiminoacetamide;
- methyl (*E*)-2-{2-[3,5-dichloro-4-(3,3-dichloroprop-2-enyloxy)phenoxymethyl]phenyl}-3-methoxyacrylate;
- methyl (*E*)-2-{2-[3,5-dichloro-4-(3,3-dichloroprop-2-enyloxy)phenoxymethyl]phenyl}-2-methoxyiminoacetate;

- (*E*)-2-{2-[3,5-dichloro-4-(3,3-dichloroprop-2-enyloxy)-phenoxymethyl]phenyl}-N-methyl-2-methoxyiminoacetamide;
- methyl (*E*)-2-{2-[3,5-dichloro-4-(3-chloro-4,4,4-trifluorobut-2-enyloxy)phenoxymethyl]phenyl}-3-methoxyacrylate;
- methyl (*E*)-2-{2-[3,5-dichloro-4-(3-chloro-4,4,4-trifluorobut-2-enyloxy)phenoxymethyl]phenyl}-2-methoxyiminoacetate;
- (*E*)-2-{2-[3,5-dichloro-4-(3-chloro-4,4,4-tri-fluorobut-2-enyloxy)phenoxymethyl]phenyl}-N-methyl-2-methoxyiminoacetamide;
- methyl (*E*)-2-[2-(4-cyclobutylmethoxy-3,5-dichlorophenoxymethyl)phenyl]-3-methoxyacrylate;
- methyl (*E*)-2-{2-[3,5-dichloro-4-(3,3-dimethylbutoxy) phenoxymethyl]phenyl}-3-methoxyacrylate;
- methyl (*E*)-2-{2-[3,5-dichloro-4-(3-methylbutoxy) phenoxymethyl]phenyl}-3-methoxyacrylate;
- methyl (*E*)-2-[2-(4-cyclohexylmethoxy-3,5-dichlorophenoxymethyl]phenyl}-3-methoxyacrylate;
- methyl (*E*)-2-{2-[3,5-dichloro-4-(2,4-dichlorobenzyloxy)phenoxymethyl]phenyl}-3-methoxyacrylate;
- methyl (*E*)-2-{2-[3,5-dichloro-4-(4-chlorobenzyloxy)phenoxymethyl]phenyl}-3-methoxyacrylate.

15. The use according to any of the claims 11-14 for the control of adults, larvae and eggs of mites and insects

which are harmful in the agrarian, civil and zoo-technical field.

16. The use according to claim 15, wherein the harmful mites and/or insects are tetranychidae (*Tetranychus urticae, Tetranychus telarius, Tetranychus cinnabarinus, Eotetranychus carpini, Panonychus ulmi, Panonychus citri*), eriophyidae (*Phytoptus avellanae, Eriophyes vitis, Eriophyes piri*) tarsonemidae (*Steneotarsonemus pallidus*), hemiptera (*Macrosiphum euphorbiae, Aphis fabae, Myzus persicae*), lepidoptera (Spodoptera spp., Heliothis spp., Chilo spp., *Carpocapsa pomonella*), coleoptera (*Leptinotarsa decemlineata, Phaedon cochleariae*), diptera (Aedes spp., Culex spp., Musca spp.).

17. The use according to any of the claims 11-14 for the control of phytopathogenous fungi such as: Helminthosporium spp., Erysiphe spp., Puccinia spp., *Plasmopara viticola,* Pythium spp., Phytophthora spp., Rhynchosporium spp., Septoria spp., *Sphaerotheca fuliginea, Podosphaera leucotricha, Pyricularia oryzae, Uncinula necator,* Venturia spp., *Botrytis cinerea,* Fusarium spp., Alternaria spp., Cercospora spp.

18. The use according to any of the claims 11-14 for the control of mites, insects and fungi which are harmful in crops of agrarian and horticultural interest, on domestic and breeding animals, in environments frequented by human

beings.

19. A method for controlling mites and/or insects and/or phytopathogenous fungi in crops of agrarian and horticultural interest, and/or on domestic and breeding animals, and/or in environments frequented by human beings, by the application of the compounds having general formula (I) according to one of the claims 1-5.

20. The method according to claim 19, characterized in that the quantity of compound to be applied varies from 10 g to 5 kg per hectare.

21. Acaricidal and/or insecticidal and/or fungicidal compositions containing as active principle one or more compounds having general formula (I) according to one of the claims 1-5.

22. The compositions according to claim 21, comprising other active principles compatible with the compounds having general formula (I), such as other acaricides/insecticides, fungicides, phyto-regulators, antibiotics, herbicides, fertilizers.

23. The compositions according to claim 21, characterized in that the concentration of active principle ranges from 1 to 90%, preferably from 5 to 50%.